Remarks

Claims 49, 53-56, 59-64 and 66-82 were pending in this application prior to entry of the above-amendments. Claims 49, 53-56, 59-64 and 66, 68, 69, 71-73, 75-77, and 79-82 have been amended. Claims 67, 70, 74, and 78 have been cancelled. New claim 83 has been added. Applicants request a three month extension of time to file this Response to Office Action and an Extension of Time Request and fee are submitted with this document.

The invention relates to agents such as Ctx, Etx, CtxB, and EtxB which are identified and employed to treat allergic and/or hypersensitivity conditions. These remarks address issues raised by the Examiner in the order presented in the Official Action and are cross-referenced to the numbered items in the Action.

Item 3. In the list of claims above, Applicants include a status identifier for every claim ever presented. The status identifiers for claims that were previously marked as withdrawn have been changed to cancelled, thus acknowledging the Examiners suggestions in paragraph 3.

Item 4. Applicants acknowledge the withdrawal from consideration of claims directed to non-elected invention. Moreover, independent claims 49, 56, 61, and 76 have been amended to remove antibodies and derivatives of antibodies, accordingly the election is moot.

Item 5. Applicants acknowledge the subject matter acted upon in the July 29, 2003 official action.

Item 6. Independent claims 49, 56, 61, and 76 have been amended to remove antibodies and derivatives of antibodies, accordingly the objection of paragraph 6 is moot.

Item 7. Claims 53-55, 59-60, 62-75 and 77-82 were objected to for use of "A", rather than "The". Each claim (still pending) has been amended as suggested by the Examiner thus obviating the objection.

Items 8/9. Claims 49, 53-56, 59-64 and 66-82 stand rejected under 35 U.S.C. §112 on the grounds that the specification does not reasonably provide enablement commensurate in scope with the claims. Specifically, the Examiner finds indefinite the recitation of: 1) *any* allergic or hypersensitivity condition and *any* antibodies and derivatives of *any* antibodies that bind to GM1; 2) the method of treating a subject for *any* "allergic or hypersensitivity condition" . . . 3) a method of treating a subject for *any* allergic or hypersensitivity condition . . *any* agent . . . *any* antibodies . . . *any* antibodies that bind to GM 1 and is not coupled to any antigen; 4) . . . any allergic or hypersensitivity condition . . . any antibodies and derivatives of any antibodies . . . not coupled to any "antigen"; 5) said method wherein the agent is CtxB or Etxb; 6) . . . any allergic or hypersensitivity condition . . . any antibodies and derivatives of any antibodies . . .; 7) any allergic or hypersensitivity condition . . . any antibodies and derivatives of any antibodies . . . any antigen/allergen.

Independent claims 49, 56, 61, and 76 have each been amended thus providing a complete response to this rejection. More specifically, amended claims 49, 56, 61, and 76 now refer to Type I allergy only, functionally limiting each claim. Support for Type I allergy can be found at Page 1, ln.24 -30 to page 2, lns, 1-5; See also, page 10, lns.15-16. No new matter has been added to this patent application. Applicants respectfully submit that each claim is allowable over the rejection as independent claims 49, 56, 61, and 76 (and all subsequent dependent claims) each particularly point out a specific group of allergy or hypersensitivity conditions well known in the art, namely Type I allergy.

In addition, independent claims 49, 56, 61, and 76, have been further amended to no longer refer to antibodies, and derivatives of antibodies. Accordingly, these claims, and subsequent dependent claims are clear.

With respect independent claims 49, 56, 61, and 76, Applicants urge that the specification does enable a person of ordinary skill in the art to use the invention commensurate in scope with these claims. The Examiner has relied heavily on the *In Re Wands* factors in concluding that the specification lacks enablement due to undue experimentation. In *Wands*, the Court ***actually*** decided "that the specification was enabling with respect to the claims at issue and found the 'there was considerable direction and guidance' in the specification . . ." See MPEP 2164.01(a). It is respectfully submitted that the instant specification also provides considerable direction and guidance in light of the fact that the independent claims have been amended to Type I allergy and the data provided in the declaration under 37 CFR 1.132 filed 6/13/03 by Neil Andrew Williams shows a working example to treating asthma, a Type I allergy. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement . . . is satisfied." *In re Fisher*, 427 F.2d. 833, 839 (CCPA 1970). *See also* MPEP 2164.01(b). One of ordinary skill in the art would clearly understand the meaning of Type I allergy. Accordingly, reconsideration is requested.

Additionally, the data provided in the declaration is predictive for any IgE mediated condition or more commonly termed Type I allergies. It is well known in the art that the OVA model used is the usual one for Type I allergies. Therefore, the data provided is sufficient for a skilled person to understand that EtxB can be used to treat an IgE mediated inflammatory response irrespective of whether the condition which caused the inflammatory response was asthma or hayfever (allergic rhinitis). Any further work to demonstrate for example that EtxB also works in other Type I conditions such as atopic eczema would require only minor modifications to the OVA model experiments already

disclosed. Accordingly, the application reasonably provides enablement commensurate in scope with the claims as amended. Reconsideration is urged.

Item 10. Claims 49, 53-56, 59-64 and 66-82 stand rejected as containing subject matter which was not described in the specification in such a way as to convey possession of the claimed invention at the time the application was filed. Applicants have amended the claims to no longer refer to allergic or hypersensitivity condition, or antibodies and derivatives of antibodies. Furthermore, the independent claims are limited to Type I allergy and four working agents Etx, Ctx, EtxB, and CtxB. As stated above, the instant specification provides considerable direction and guidance in light of the fact that the independent claims have been amended to type I allergy and the data provided in the declaration under 37 CFR 1.132 filed 6/13/03 by Neil Andrew Williams shows a working example to treating asthma, a type I allergy. Applicants believe that the declaration illustrates that the claimed subject matter was in Applicants' possession at the time the application was filed.

Items 11/12. Applicants acknowledge the obligations under 37 CFR 1.56.

Item 13. Claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80 stand rejected under 35 U.S.C. §103 as obvious at the time of invention over WO 95/10301 or Tamura, in view of WO 97/02045 or Nashar et al.(1996), previously of record. Applicants respectfully request that the Examiner reconsider the rejection in light of the amendments above and commentary below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See MPEP 2143.

Applicants strongly urge that there is no motivation to combine WO 95/10301 or Tamura et al (which relate to conjugated molecules) with WO 97/02045 or Nashar et al. Moreover, the Examiner has not shown any motivation to remove the antigen, or that doing so would produce a therapeutic or successful method.

WO 95/10301 discloses an immunological tolerance inducing agent having a mucosa binding molecule linked to a specific tolerogen, and relates only to coupled molecules. According to the description (see page 8, lines 26-32) the findings challenge the established opinion that mucosal administration of these coupled molecules induce immune responses. The skilled person would therefore not consider or be motivated to use uncoupled molecules as this was not the issue under investigation.

Tamura only teaches EtxB coupled to antigen. It is clear that the EtxB is acting as a carrier (see page 228, column 1, last line of first full paragraph) so the skilled person would not consider using an uncoupled version. Moreover, the amended claims in the present application have been limited to Type I allergy. This sharply contrasts the last example in Tamura "Abrogation of LTB-induced nasal suppression by LT". This experiment does not in any way show that EtxB alone or with antigen would be useful to treat type I allergies. The DTH data (figure 2) indicate that the DTH response with EtxB + OVA is equivalent to that which received PBS alone (top bar versus fifth bar). Statistically significant results in this figure are marked with a star. There is no star in the EtxB+OVA column. Furthermore, the authors do not claim that LTB + OVA has any effect, but focus solely on the LTB-OVA conjugate. The whole point of the experiment is to show that Etx abrogates the LTB-OVA induced suppression, which teaches away from the subject matter of the present invention.

WO 97/02045 relates to the use of agents in the treatment of autoimmune disease, human leukemias of a T cell origin, transplant rejection or GVHD. It does not teach or suggest their use in the treatment of allergies, let alone in the treatment of IgE-mediated Type I allergies which is now required by the amended claims. The Examiner has highlighted the reference to OVA on page 16 of WO 97/02045. In Example 1 of the

reference, it was shown that CD8+ cells were depleted in response to EtxB. To ascertain whether EtxB can induce depletion of CD8+ T cells responding to an antigen other than EtxB, OVA was used as an experimental antigen (see page 36, line 27 to page 37, line 24). OVA is an extremely common experimental antigen. Its capacity to act as an allergen is not mentioned and is not relevant to the experiment. The experiment does not in any way teach or suggest the use of EtxB (with or without antigen/allergen) to treat Type I allergies.

Nashar et al. relates to receptor binding for EtxB, using a receptor-binding mutant (G33D). It does not teach or suggest the use of EtxB in the treatment of allergies.

The Examiner has not shown any motivation to remove or uncouple the antigen, or that doing so would produce a therapeutic or successful method, and the prior art offers no suggestion to pursue the desired therapeutic agents. Hence there is no likelihood of success demonstrated by the Examiner of providing a therapeutic result using the claimed method. Accordingly the independent claims are not obvious. Moreover, it is respectfully submitted that the Examiner is improperly using hindsight reasoning to assert obviousness.

Item 14. The Examiner has objected to claims 54, 60, 64, 66-70, 72-75, 77-78, and 81 and 82 as under 35 U.S.C. §103 as obvious at the time of invention over WO 95/10301 or Tamura each in view of WO/97/02045 or Nashar as applied to claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80 and further in view of Roitt and Patterson. The rejection is respectfully traversed, and Applicants respectfully request that the Examiner reconsider the rejection in light of the amendments made to each independent claim.

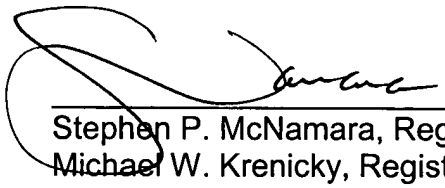
In light of the amendments made herein, it is respectfully requested that the Examiner reconsider the prior responses. Roitt *et al.* describes hypersensitivity in general terms. Patterson *et al.,* attempted to determine if human peripheral blood lymphocytes cultured in vitro could be used to study the pharmacological effect of agents on IgE pro-

duction. The prior response to the previous objections based on these references is hereby incorporated by reference. Alone or in combination, the cited references do not solve the problem of the amended claims by providing a method of treating subjects in need thereof for Type I allergy. They do not teach a solution for treating type I allergy as required by the amended claims. These refrences would not be consulted by a skilled worker looking for ways to provide a therapeutic agent in a new treatment for subjects in need of treatment for Type I allergy. Type I allergy is now required by claim 61, and claim 61 is not obvious.

Finally, in light of the fact that the Examiner is using references that would not be consulted to solve the problem of the claimed invention, it is respectfully submitted that the Examiner is once again using improper hindsight reasoning. The independent claims are not obvious, and reconsideration is requested.

If the Examiner has any questions regarding this Response, the Examiner is invited to call Michael Krenicky at (203) 324-6155. Early favorable action is respectfully requested.

Respectfully submitted,



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